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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,221	07/15/2003	Gary A. Koppel	22064-71990	8706

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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
05/21/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

indocket@btlaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/620,221	KOPPEL, GARY A.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *1,7-10 and 12-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-6 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17 are presented for examination.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's payment and submission filed March 4, 2010 was received and entered into the present application. Accordingly, prosecution has been reopened.

Applicant's Terminal Disclaimer filed March 4, 2010 has been received and entered into the present application. Due to the acceptable nature of the Terminal Disclaimer, the obviousness-type double patenting rejections over U.S. Patent Nos. 6,426,342; 6,610,681; and 6,627,625 are withdrawn.

Claims 1-17 remain pending. Claims 1, 7-10 and 12-17 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b). Claims 2-6 and 11 are under examination.

Applicant's arguments, filed March 4, 2010, have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement

(New Grounds of Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-6 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the

written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In particular, the specification as originally filed fails to provide adequate written description for (1) an amount of clavulanic acid salt(s) or active ester form(s) thereof that hydrolyze *in vivo* to clavulanic acid effective to modulate neurogenic carboxypeptidase or transpeptidase activity in the brain (claim 11) or (2) an amount of clavulanic acid salt(s) or active ester form(s) thereof that hydrolyze *in vivo* to clavulanic acid effective to provide a cognition enhancing concentration of clavulanic acid in the brain (claim 2).

Applicant provides various functional descriptions of the amount of the clavulanic acid compound(s) to be administered (i.e., that it is effective to modulate neurogenic carboxypeptidase or transpeptidase activity in the brain or that it is effective to provide a cognition enhancing concentration of clavulanic acid in the brain), but has failed to provide any description of the particular amounts, or a range of amounts, that are actually functional to achieve the effect as instantly claimed and would provide adequate written description of these claimed genera of amounts of clavulanic acid salt(s) or active ester form(s) thereof that hydrolyze *in vivo* to clavulanic acid that are capable of modulating neurogenic carboxypeptidase or transpeptidase activity in the brain or that are effective to provide a cognition enhancing concentration of clavulanic acid in the brain that Applicant was actually in possession of, and intended to be used within the context of the present invention, at the time of the invention.

Applicant's instant specification provides disclosure of amounts of clavulanic acid *per se* that are effective to inhibit neurogenic NAALADase (defined at p.1 of the instant specification as including transpeptidases and/or carboxypeptidases), such as, e.g., less than 1 microgram/kg body weight when administered i.p. (p.24, l.25-27) or about 0.1 to about 10 mgs per dose when administered orally (p.25, l.6-7). Applicant further teaches that the range of effective dosage levels of the disclosed inhibitors when

used for treating cognitive disorders will depend upon patient body weight, affinity of the inhibitor for the target neurogenic protease, the blood-brain barrier transport characteristics of the active compound, mode of administration and optional use of available drug formulations/conjugation technologies available for enhancement of blood-brain barrier transport (p.24, l.27-33).

However, though such disclosure has been fully and carefully considered, it fails to provide any description of the amounts of the instantly claimed clavulanic acid salt(s) or active ester form(s) of clavulanic acid that hydrolyze *in vivo* to clavulanic acid that may be employed to achieve these instantly claimed functions. Accordingly, the instant specification appears to lack any specific description of the amounts that would fall within the instantly claimed genera of amounts effective to modulate neurogenic carboxypeptidase or transpeptidase activity in the brain or amounts effective to provide a cognition enhancing concentration of clavulanic acid in the brain such that these amounts could be immediately envisaged and/or readily identified. Absent such description, one of skill in the art would have to undertake extensive hit or miss testing to determine the full scope of the genera of amounts claimed, which is clearly indicative of the fact that Applicant was, in fact, not in possession of the full scope of amounts effective to achieve the instantly claimed function(s). This is because Applicant cannot logically be in possession of that which he has yet to identify.

Absent any clear description of even an exemplary amount that is effective to achieve the function(s) instantly claimed, it remains that Applicant has failed to clearly define the metes and bounds of the claimed genera of amounts. While it is duly noted that the claimed genus is limited to those amounts capable of functioning in the claimed manner, it remains that Applicant has not appropriately defined the metes and bounds of the genus even when limited by function. The specification provides no disclosure beyond the generic disclosure of the required function that would correlate a particular amount to performance of the claimed function that would be readily identifiable to one of skill in the art. Further, Applicant has failed to establish on the record that the state of the art was sufficiently well-

developed that one of ordinary skill in the art at the time of the invention would have immediately envisaged the specific amounts that would perform the claimed function(s) in the instant specification. In other words, the present specification provides no disclosure beyond the generic disclosure of the required functions that would provide a means for identifying the amounts of the instantly claimed clavulanic acid salt(s) or active ester form(s) of clavulanic acid that hydrolyze *in vivo* to clavulanic acid that would have been amenable for use in the present invention, absent factual evidence to the contrary. Furthermore, it has been held that a wish or plan for obtaining the invention as claimed does not provide adequate written description of the invention. Rather, a precise definition, such as by structure, formula, chemical name or physical properties or a combination thereof (or, in the instant case, disclosure of at least an exemplary amount effective to provide the plasma concentration(s) claimed), is required. Please reference, e.g., *Univ. of Rochester v. G.D. Searle & Co.,* 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004).

While it is recognized that adequate written description of a limitation is not required to be stated *in haec verba* in the specification or claims as originally filed, adequate written support for claim limitations must arise from either an explicit or implicit suggestion by the disclosure to show that such a concept as claimed was actually in possession of Applicant at the time of the invention. For the reasons provided *supra*, Applicant has failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means that fully set forth the claimed invention, in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of (1) an amount of clavulanic acid salt(s) or active ester form(s) thereof that hydrolyze *in vivo* to clavulanic acid effective to modulate neurogenic carboxypeptidase or transpeptidase activity in the brain (claim 11) or (2) an amount of clavulanic acid salt(s) or active ester form(s) thereof that hydrolyze *in vivo* to clavulanic acid effective to provide a cognition enhancing concentration of clavulanic acid in the brain (claim 2).

Accordingly, the claims are considered to lack sufficient written description and are properly

rejected under 35 U.S.C. 112, first paragraph.

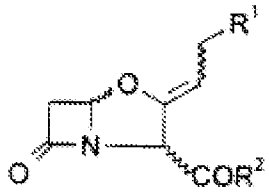
Claim Rejections - 35 USC § 103 (New Grounds of Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

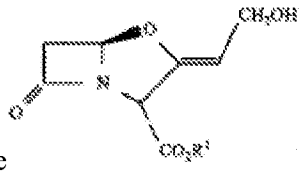
Claims 2-6 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tew et al. (WO 97/10247; 1997) in light of Cole et al. (U.S. Patent No. 4,110,165; 1978), cited to show a fact, and in view of Yoshida et al. (U.S. Patent No. 4,690,949; 1987) and Pfister et al. (U.S. Patent No. 5,889,007; 1999).

Tew et al. teaches clavulanic acid derivative compounds of the structure



(abstract; p.2, l. 15-20), wherein R^1 is selected from, *inter alia*, OH, etc., and R^2 is selected from, *inter alia*, OC_{1-6}alkyl, etc., p.2, l.16-23). Tew et al. teaches that the compounds function as inhibitors of lipoprotein associated phospholipase A_2 (Lp-PLA_2) and are, therefore, useful in a method for treating a disease state associated with the activity of the enzyme Lp-PLA_2, and include, *inter alia*, disorders that involved lipid peroxidation in conjunction with Lp-PLA_2 enzyme activity, such as, *inter alia*, Alzheimer's disease (p.4, l.5-14 and 18-24). Tew et al. further teaches that the compounds may be formulations into liquid formulations, tablets, capsules, parenteral compositions, suppository formulations, etc. (p.5, l.1-26), wherein the daily dosage regimen for an adult patient may be an oral dose between 1 mg and 500 mg, preferably between 1 mg and 250 mg, or an intravenous, subcutaneous or

intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound, administered from 1 to 4 times per day and suitable for a period of continuous therapy, such as for a week or more (i.e., which is considered to meet Applicant's effective amount(s) of instant claims 2 and 11, absent factual evidence to the contrary; p.5, l.30-36).

Cole et al. is cited for its teaching that esters of clavulanic acid show an enhanced tendency to hydrolyze to clavulanic acid under mild conditions, such as simple alkyl esters, such as the methyl ester, slowly hydrolyze to clavulanic acid in water buffered to pH 7 (col.5, l.66-col.6, l.3). Cole et al. teaches that esters of the structure  , wherein R^1 is a hydrocarbon group of 1-9 carbon atoms that may be further optionally substituted, hydrolyze to clavulanic acid under mild conditions (col.6, l.3-21). Note that these clavulanic acid esters disclosed by Cole et al. are identical to those esters disclosed by Tew et al. (see *supra*, wherein R^1 is selected from, *inter alia*, OH, etc., and R^2 is selected from, *inter alia*, OC_{1-6}alkyl, etc.; p.2, l.16-23) and, therefore, would also function to hydrolyze to clavulanic acid upon administration, particularly under the mild pH conditions of the body, absent factual evidence to the contrary and in view of the teachings of Cole et al.

Tew et al. fails to teach (1) that the patient suffering from Alzheimer's disease also suffers from dementia (claim 3) or (2) the additional administration of the P-glycoprotein efflux pump inhibitor (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}quinoline (claims 5-6).

Yoshida et al. teaches that dementia can be classified into clinical types depending upon the etiology and include Alzheimer's disease, senile dementia of Alzheimer type, or dementia due to cerebral vascular diseases (col.2, l.34-37).

In view of such teachings, it would have been *prima facie* obvious to one of ordinary skill in the

art at the time of the invention that the disclosed compound(s) of Tew et al. for the treatment of Alzheimer's disease *per se* would have been reasonably expected to exert the same or substantially equivalent efficacy in the treatment of dementia in a patient in need of such treatment because: (1) the composition of Tew et al. was known to have efficacy in treating patients that suffer from Alzheimer's disease *per se* and (2) a proportion of patients therein that have Alzheimer's disease also suffer from dementia, as evidenced by Yoshida et al. Tew et al. provides the clear teaching that the instantly claimed clavulanic acid ester(s) is, in fact, effective for treating all Alzheimer's patients, i.e., 100% of patients with Alzheimer's disease, without exclusion. Of this entire population of Alzheimer's patients, Yoshida et al. provides the factual extrinsic evidence demonstrating that a subpopulation of Alzheimer's disease patients suffers from dementia. Accordingly, the teaching of Tew et al. to use the claimed clavulanic acid ester formulation for treating any Alzheimer's disease patient is a clear suggestion to use it in any subpopulation of Alzheimer's patients, such as those patients suffering from dementia, with the reasonable expectation of the same (or at least substantially equivalent) level of efficacy in treating this subpopulation of patients with dementia as would be expected in the treatment of Alzheimer's disease patients *per se*. Furthermore, since products of identical composition cannot have mutually exclusive properties when administered under identical conditions, or, as in the present case, the same host, whatever effect(s) the instantly claimed clavulanic acid ester compound has in treating dementia must necessarily be present in the method disclosed by Tew et al., absent factual evidence to the contrary.

Pfister et al. teaches 10,11-methanodibenzosuberane derivative compounds, such as, *inter alia*, (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-quinoline (Ex.6, compound (b) at col.20, l.17-20) for use in enhancing the bioavailability of a pharmaceutically active agent by administering to a mammal an effective amount of a compound of the disclosed formula [of which (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-quinoline is specifically exemplified in Ex.6, compound (b) at col.20, l.17-20]

sufficient to increase permeation of the active agent through the blood-brain barrier (col.2, l.23-29). Pfister et al. teaches that chemosensitizing agents (such as those disclosed therein) interact with the P-glycoprotein drug efflux pump by blocking the pump, which results in enhanced permeation of active agents through the blood brain barrier (col.1, l.53-61).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to use and administer the compound (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-quinoline in combination with the clavulanic acid derivative compound of Tew et al. for the treatment of patients suffering from Alzheimer's disease because such a compound was known to enhance the bioavailability of pharmaceutically active agents by increasing permeation of the agent through the blood-brain barrier, as evidenced by Pfister et al. Such a person would have been motivated to do so in order to increase plasma concentrations of the active agent to effective levels and also to enhance penetration of the clavulanic acid compound through the blood brain barrier into the brain to treat damaged neuronal cells.

Conclusion

Rejection of claims 2-6 and 11 is proper.

Claims 1, 7-10 and 12-17 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Primary Examiner, Art Unit 1614

May 18, 2010